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(54) Title: A DRESSING MATERIAL COMPRISING A PHARMACOLOGICAL ACTIVE AGENT ENTRAPPED IN LIPOSOMES (57) Abstract Liposomes containing a pharmacologically active agent may be entrapped in an alginate matrix and formed into films, fibres, foams or clots to provide wound dressings.		

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A dressing material comprising a pharmacological active agent entrapped in liposomes.

The present invention relates to dressing materials and to processes for their production.

The healing properties of alginate gums have been known for some time and have been exploited for instance in dental treatments (Blaine, Annals of Surgery, Vd125(1), 102-114, (1947) and Rumble, British Dental Journal, 14 April 1949, pages 203-5), haemostasis in neuro surgery (Oliver et al British Journal of Surgery, 307-310 (1950)) and in wound dressings (Gilchrist et al, Biomaterials, 4, 317-320 (1983)).

Liposomes are known for encapsulating biologically active materials but are notoriously difficult to handle in practice, are readily disrupted by shearing forces and have not lived up to the expectations which they initially aroused. Various proposals have been put forward for stabilising liposomes and a particular example which may be mentioned is the microencapsulation described in International Patent Application W0-A-87/01587. The materials described there enable the release profile of a biologically active material (a payload) entrapped within liposomes to be controlled but are relatively rigid and brittle and thus are not well suited to use in dressings.

It has now surprisingly been discovered that it is possible to entrap liposomes in films and fibres of a hydrocolloid matrix in order to produce medicated wound dressing materials and drug delivery systems in which the

- 2 -

integrity of the liposomes is preserved and which are flexible and conformable.

Accordingly the present invention provides a dressing material comprising a pharmacologically active agent entrapped in liposomes, the liposomes being encapsulated in a hydrocolloid matrix.

Preferably the dressing material is in the form of a film or is a fibrous material. Fibrous materials include threads or yarns, woven and non-woven webs, spun wools and the like. The invention also provides a liquid formulation comprising a hydrocolloid matrix material and liposomes in aqueous suspension for use in forming foams, clots or films in situ together with a gelling agent (such as a calcium salt solution when the matrix is an alginate) for cross-linking the liquid formulation during or after application of the hydrocolloid/liposome formulation or for admixture with the hydrocolloid/liposome formulation shortly before formation of the foam, clot or film. Foams, clots and films formed in this manner are dressings according to the invention.

In one aspect the dressing material is intended for internal or external application as a wound dressing to provide a barrier and to promote healing and the payload will usually be a drug intended to promote healing or an antibiotic intended to treat or prevent infection of the wound.

In another aspect the dressing will be intended as a

- 3 -

delivery system and such materials will normally be applied topically but may be applied internally to release a pharmacologically active agent to an appropriate site in the body. The payload may then be any active agent which is to be administered topically or locally internally.

Suitably the matrix is a gelled alginate salt matrix such as calcium alginate and it may optionally be plasticised using, for instance, glycerol.

The films and fibres may be prepared and dried for subsequent use in the dry state or after rehydration, or they may be maintained moist in a suitable aqueous medium such as a sterile buffer solution.

The wound dressing materials will always be sterile and this may be achieved by use of sterile ingredients which are handled in a sterile environment or by post-sterilisation for instance by irradiation. Generally the materials will also be non-pyrogenic depending upon the intended end use.

The films and fibres may be of any convenient dimensions and films will normally be at least 1 cm in width and length, possibly up to 0.5m or even 1m or more for special applications such as in dressing burns. The fibres will be of any convenient length and will usually be chopped into such lengths from longer staples. The thickness of the films and the cross-sectional size of the fibres will typically be somewhat greater than the diameter of the encapsulated liposomes. The upper limit on the thickness of the films and cross-section of the fibres will depend partly

- 4 -

on the desired end-use but mainly on considerations of flexibility. Typically films will be of the order of 1mm or less in thickness and fibres will have similar diameters.

Alginic acid is a naturally occurring polysaccharide extractable from brown seaweed (Phaeophyceae). It is composed of varying proportions of beta-D-mannosyluronic and alpha-L-gulosyluronic acid connected by beta-1-to-4 linkages. The alginic acid is usually converted to mixed calcium/sodium salts. Calcium alginate is insoluble in aqueous solutions, while the sodium salt is highly soluble. Upon exposure to a calcium salt at sufficient concentration, the soluble sodium alginate is converted to an insoluble, but hydrated, gel. This useful property of alginate is the basis for its use in the preparation of films or filaments. In addition, alginates are haemostatically active materials capable of stimulating the contact-activation stage of the clotting cascade, and are therefore useful in the control of bleeding. Published studies have shown that alginate gels promote healing of wounds and that alginate gels are compatible with a wide variety of pharmaceutically active compounds. When in prolonged contact with body tissues, alginates break down to monosaccharides and are totally resorbed (Blaine, 1947; Rumble, 1949; Gilchrist and Martin, 1983). Finally, our previous work (International Publication Number: WO 87/01587) demonstrates that calcium alginate stabilizes liposomes in both the hydrated state by limiting diffusion and opportunities for liposome-liposome

- 5 -

interactions, and in the anhydrous state by promoting retention of the bilayer configuration in the absence of water.

Alginates are available in various grades that may be prepared to yield specific properties for specific applications. High molecular-weight alginates yield stiffer gels than low molecular-weight alginates. Gel viscosities may also be controlled by the concentration of alginate and its ratio of sodium:calcium salts.

Control of the gelling mechanism of sodium alginate by calcium salts permits the formation of alginate mixtures containing high concentrations of other excipients or active ingredients. However, due to the high permeability of the gels to water, calcium-alginate gels can not be utilized to encapsulate low molecular-weight water-soluble materials.

The result, which arose from a blending of modern liposome technology and film-forming technology with the techniques of microparticle and microcapsule formation, is a liposomal payload which is protected from dissolution by hydrodynamic shear and which retains its integrity in the presence of emulsifying agents. Encapsulation of liposomes within a matrix of alginate/gelatin yields a carrier-vehicle which is fully biodegradable, non-toxic, and capable of transporting both hydrophilic and hydrophobic solutes.

Hereafter the term "lipofilm" will be used to denote a product according to the invention. Those lipofilms

- 6 -

wherein the matrix comprises an alginic salt and a plasticiser are designated Type I lipofilms and those wherein the matrix comprises an alginic salt only are designated Type II lipofilms.

In both Type I and Type II lipofilms the payload may be any hydrophilic or hydrophobic protein or pharmacologically active agent or a mixture of such components whilst the liposomes may be composed of one or a mixture of lipids selected to entrap the payload and provide desired release characteristics. Here, it is the use of alginate/plasticiser as a matrix which is particularly important.

The composition of the entrapped liposomes may be controlled to achieve controlled release of the payload as a function of temperature, pH, ion concentration or the presence of specific perturbants. The liposome may be comprised of any bilayer- or micelle-forming lipid. All lipids in these categories may be suitable, regardless of their combined or individual permeability, since they may be combined to achieve the desired payload-release kinetics. Permeation of the payload through the barrier of the lipofilm may be regulated by the grade of alginate, by the ratio of alginate to gelatin or other hydrocolloid, by the absolute concentration of liposome and payload in the film, and by the chemistry and extent of cross-linking.

The composition of the liposomal components of Type I and Type II lipofilms may be varied to suit specific applications. Liposomes may be prepared from essentially

- 7 -

any class of phospholipid; variability in phospholipid class derives from each of the hydrophobic and hydrophilic domains of these amphipathic molecules. Individual phospholipids may be chosen based upon their nutritional value and/or their permeability. Permeability of individual liposome preparations is dependent upon: extent of unsaturation, presence or absence of sterols, the temperature of their gel-liquid-crystalline phase transition, the ionic- and pH-dependence of their lamellar-hexagonal transition, the temperature-dependence of non-bilayer configurations, and the extent of monomer conversion of polymerizable phospholipids (Hayward et al., 1985).

In addition to composition, the configuration of liposomal preparations may be varied to suit specific applications. A great variety of liposomal preparatory methods are available which differ in: ease of production, solvent and equipment requirements, and tolerance for different lipid classes. The liposomes produced by these different methodologies vary in: number of lamellae, aqueous volume enclosed per mole of phospholipid, resistance to shear, entrapment efficiency, diameter, and resistance to fusion/aggregation/precipitation (reviewed by Gregoriadis, 1984). The choice of liposomal configuration will be dictated largely by the intended application and the required profile of payload release.

In both Type I and Type II lipofilms the liposomes may be uni- or multilamellar, and they may be of any

- 8 -

suitable size appropriate to the intended use of the lipofilm and the materials used to form the liposomes.

As regards Type I lipofilm, the matrix comprises an alginate salt, of 1 to 5 percent, and a plasticiser, such as glycerol or dimethylsulphoxide, in a ratio of 99:1 to 90:10 by volume. Inclusion of glycerol or dimethylsulfoxide (DMSO) in the cross-linked lipofilm permits the dehydration and rehydration of the films without loss of liposome latency. The percentage and grade of alginate may be modified to modulate the permeability and rate of absorption of the barrier posed by the matrix. Various soluble and insoluble salts of alginate may be employed; preferred soluble salts include sodium alginate and preferred insoluble salts include calcium alginate. A large number of liposomes will be encapsulated by the hydrocolloid matrix of each lipofilm.

Type I lipofilms would ideally be suited for the formation of films containing liposomal encapsulated pharmaceutically active substances which are to be lyophilized. The incorporation of glycerol yields an absorbable film which is plastic-like in its dry state with a fair degree of tensile strength while exhibiting none of the brittleness of dried calcium alginate. Type I lipofilms may be designed to deliver the drug to any particular site of a wound or burn providing it with a time-release, multi-barrier drug delivery system that is flexible and forms an impermeable cover. Due to the nature of the alginate

- 9 -

matrix, such a film would enhance tissue repair, arrest capillary haemorrhage and absorb exudate from the site of application. Ease of packaging, storage and use of such a dried lipofilm would allow for the immediate application to a wound by a paramedic at the scene of a crisis.

Turning to Type II lipofilms, the matrix would be composed of an alginate salt, of 1 to 5 percent. As in Type I lipofilms, the percentage and grade of alginate may be varied to modulate the rate of absorption; the payload the liposome carries may be varied according to the appropriate use of the specific lipofilm product. Wools and gauzes could be formed and supplied in dry packages, while films and clots could be formed in situ.

A prime example of the use of such lipofilms in the form of wool would be in dental applications. The lipofilm payload would be comprised of an appropriate antibiotic, e.g. penicillin, combined with a non-steroidal anti-inflammatory drug, e.g. aspirin, to be used in the arrest and prevention of post-extraction haemorrhage in the tooth socket. Thus, such a formulation would provide a multi-barrier, time-release drug system which would be totally absorbed into the tooth socket with no harmful local effect on the tissue or delay in healing of the wound.

One application for the formation of a clot in situ would be in the treatment of ear infections. In such a case a codispersion of sodium alginate containing the liposomes would be introduced into the ear canal. A solution of

- 10 -

calcium chloride would be introduced causing the subsequent formation of the clot within the ear canal in the exact conformation of the canal. Thus, medication would be continuously released directly at the site of wound or infection and the alginate would be totally absorbed eliminating the necessity for removal of any packing at a later date. Lipofilm wool may find application as wound dressings or dental packing. In the latter application, ideal payloads would include antibiotics such as tetracycline and penicillins with or without addition of non-steroidal anti-inflammatory drugs.

The present invention also provides a process for producing lipofilms whereby the process comprises:

- a) entrapping the payload in liposomes, and,
- b) encapsulating the liposomes in a hydrocolloid matrix.

In step (a) the liposomes may be formed by conventional processes such as those described by Gregoriadis (1984).

Step (b) is accomplished by admixing the liposomes with an aqueous solution of the hydrocolloid matrix material. Curing or polymerization of the lipofilm matrix may be accomplished by chemical means as in the calcium ion-mediated precipitation of sodium alginate or by aldehyde cross-linking. The desired shape of the lipofilm may be achieved by using the appropriate extrusion method.

In a preferred embodiment of this process the payload is entrapped in the liposomes by reverse-phase

- 11 -

evaporation and the liposomes are then separated from untrapped material and washed. The liposomes are then mixed with the hydrocolloid matrix material in aqueous solution and either extruded into a curing bath or spread on a support such as a porous support, a filter or a sheet of glass to form a film and submerged into a curing bath or otherwise contacted with curing solution. The curing bath or solution preferably contains a calcium chloride solution at a concentration in the range of 1 to 20 percent (weight/volume) and the lipofilms ride in the curing bath for about five minutes in order to harden the alginate matrix. The viscosity, texture, tensile strength and rate of absorption is dependent upon the duration of curing, the concentration and type of curing agent, the molecular weight and concentration of sodium alginate. The absorption rate further depends on the physical form and bulk of the product, thus alginate gauze or clots would be absorbed slower than thin films. After formation and curing, the lipofilms are separated from the curing bath and washed prior to storage or in the case of Type I films prior to lyophilization. An interesting variation is made possible by the use of ultrafiltration to wash the lipofilm. Ultrafiltration membrane may be chosen with specific molecular-weight cut-offs. Molecules with molecular weights in excess of the cut-off will not pass through the membrane, while those molecules with molecular weights below that value will pass freely. Cross-linked lipofilms formed and

- 12 -

cured on an ultrafiltration membrane may be loaded with payloads in the aqueous external volume (the aqueous volume within the film external to the liposomes) by adding the payload to the wash solution. As the wash solution is forced through the membrane under pressure, the payload will be concentrated in the lipofilm if the payload molecular weight is greater than that of the membrane cut-off. In this manner, lipofilms may be prepared with two different water-soluble payloads: a low-molecular weight payload encapsulated only within the intraliposomal volume, and a high-molecular weight payload concentrated only within the extraliposomal volume.

We have discovered that pharmacologically active agents or nutritional components can be delivered in liposomes comprising nutritionally or pharmacologically active lipids, the liposomes being protected by microencapsulation in a hydrocolloid matrix, and that certain hydrocolloid matrices containing alginate offer particular advantages in ease of encapsulation and control in release of pharmacological, nutritional or other payloads from the entrapped liposomes (International Publication Number: WO 87/01587, which describes Lipogel Microcapsules). With the present invention, Lipofilm Multiple Barriers, we describe the extension of a 3-dimensional microencapsulation system to form a novel 2-dimensional system which, due to the formation of planar films, is suitable for use in wound dressings.

- 13 -

The invention also provides dressings as defined above, and formulations for in situ preparation of such dressings, for use in a method for treatment of the human or animal body by surgery or therapy and methods for treating human and non-human animals comprising external or internal application of a dressing as defined above. In therapeutic methods the dressing applied or formed in situ will contain an effective non-toxic amount of a pharmacologically active agent entrapped with the liposomes.

Further details concerning the production and use of the fibres will be apparent from the following Examples which are not intended to limit the scope of the invention in any way.

EXAMPLE 1

a) Production of Liposomes

Liposomes were constructed using dicetylphosphate and a) soy lecithin or b) dipalmitoylphosphatidylcholine (DPPC) (1:8, mole:mole). The lipid(s) was initially dissolved in 5 ml of chloroform in a 50 ml conical flask and dried to a thin film by evaporation under nitrogen. A solution of 0.25 M 6-carboxyfluorescein (6-CF; Eastman) was prepared in distilled water and the pH was adjusted to 7.4 using NaOH (Senior and Gregoriadis, 1984). This dye is self-quenching at this concentration and is used as an aqueous marker for liposome leakage. Additionally, 6-CF may be considered as an analogue for biomedical payloads. Twenty-five mls of 6-CF were added to the lipid and the

- 14 -

conical flask was heated to 40°C. The 6-CF-lipid mixture was flushed with nitrogen for 3 minutes, 3 glass beads were added, the flask was stoppered, and mixed with a vortex mixer for 3 minutes to form multilamellar vesicles (MLV's). The suspension of MLV's was sonicated using a bath sonicator (Laboratory Supplies, N.Y.) for 15 minutes. The liposomes were separated from un-entrapped material by passing the suspension through a Sepharose CL-6B (Pharmacia) column (1 cm x 20 cm) (Senior and Gregoriadis, 1984).

b) Production of Type I lipofilms

Liposomes prepared as described above were entrapped in calcium alginate-glycerol as follows. Sodium alginate (1% w/v) was added to distilled water slowly while the mixture was rapidly stirred on a combination hot and stir plate at 40 degrees C until completely dissolved. The mixture was allowed to cool to 4 degrees C. Following cooling, the liposomes (1:1, v/v) and the glycerol (10% v/v of total liposome-alginate mixture) were stirred into the alginate solution using a stir bar. After the liposomes and glycerol were added to the alginate polymer, the solution was poured and spread to a thin layer on a glass plate. The plate, with the thin film, was totally submerged into a curing bath of calcium chloride (2.2% w/v) and allowed to harden for five minutes. The film was removed from the curing bath and submerged in a bath of distilled water. The film was then transferred to a saran film, rolled up and lyophilized.

- 15 -

c) Production of Type II lipofilms

Liposomes are produced according to part (a) above and encapsulated in alginate without the added glycerol according to part (b) above. After washing with water these gels are not lyophilized. Instead, they are stored in distilled water with kathon (0.05% v/v) at 4 degrees C. Kathon is added to prevent bacterial growth.

EXAMPLE 2

a) Polymer-Supported Lipofilms

Liposome dispersions and sodium alginate solutions are prepared as described under "Production of Type I or Type II Lipofilms". After mixing, the liposome-alginate mixture may be cross-linked on several different types of porous matrices.

i) Polycarbonate Filters

Polycarbonate filter assemblies (available from Nalgene Corp) are assembled after first loading the lower reservoir with calcium chloride solution (2.2% w/v). The level of solution is raised to maintain contact between the solution and the polycarbonate filter which forms the base of the upper reservoir. A thin layer of the liposome-sodium alginate mixture is deposited on the upper face of the polycarbonate filter. Incubation overnight allows sufficient exchange of calcium and sodium to cross-link the alginate fully.

The cross-linked film may be washed and removed from the filter by repeated addition of deionized water to the

- 16 -

upper reservoir. Alternatively, the film may be washed by drawing deionized water through the film by the application of a vacuum to the lower reservoir. The advantage of the latter method is that washing is completed more rapidly and involves the internal compartment of the matrix as well as the external surface.

ii) Nucleopore and Other Ultrafiltrating Membranes

Ultrafiltrating membranes, available from the Amicon Corp (Boston MA), may be obtained with hydrophobic or hydrophilic surfaces. Hydrophobic ultrafilters were found to repel the liposome-alginate mixtures and were therefore unsuitable as lipofilm supports. Hydrophilic membranes were wetted by the liposome-alginate mixture and adsorbed the cross-linked lipofilm well.

The ultrafiltrating membrane (25 mm diameter) was placed in a petri dish of slightly larger diameter (35 mm). The liposome-alginate mixture was layered onto the surface of the membrane with care to avoid spillage over the membrane edge. A solution of calcium chloride (10% w/v) was added by a pipette placed against the inside wall of the petri dish. Care must be taken to avoid disturbing the adsorbed liposome-alginate dispersion. A high concentration of calcium chloride solution was required because the ratio of volumes between the calcium and alginate solutions was low. After initial "skinning" of the lipofilm surface, the membrane-supported lipofilm is transferred to a large volume (100 ml) of calcium chloride solution (2.2%).

- 17 -

Washing of the cross-linked film was achieved by dipping the membrane into several volumes of distilled water. Alternatively, the adsorbed lipofilm could be assembled in the Amicon Concentrator unit and washed by passage of water through the membrane under nitrogen pressure (less than 20 p.s.i.).

iii) Lipofilm Supported by Cellulosic Filter Pads

The liposome-sodium alginate mixture was poured into a small trough (35mm petri dish). In a separate dish, a 35mm Whatmann (No 1) filter pad was saturated with a solution of calcium chloride (2.2% w/v). Care was exercised to avoid over-saturation of the pad. The pad was then placed carefully on the surface of the liposome-alginate mixture for one minute. During this time, a thin layer of lipofilm became partially cross-linked and adsorbed to the surface of the filter paper. (Longer incubation times permitted diffusion of the calcium ions away from the filter pad through the liposome-alginate mixture, producing a non-adsorbent, partially polymerized and heterogeneous "block" of calcium alginate). The filter paper with adherent lipofilm was then transferred to a curing bath of calcium chloride (2.2% w/v). An additional incubation period of 5 to 20 minutes produced an integral film which could be washed in ionized water and separated from the filter support.

- 18 -

EXAMPLE 3Formation of Lipofilm Wools or Gauzes.

Lipofilm may be cross-linked as a continuous thread by extrusion of the liposome-sodium alginate mixture (Type I) under the surface of a solution of calcium chloride (2.2% w/v). Extrusion was accomplished through a 50-ml syringe or with the aid of a peristaltic pump. Positive pressure must be exerted continuously throughout extrusion to prevent diffusion of calcium ions into the sodium alginate reservoir.

After allowing the strands of lipofilm to harden fully (5 - 20 minutes), washing was accomplished under a stream of deionized water. The strands were drained and compressed gently between two glass plates. The sandwich was frozen (-80 degrees C) and lyophilized to produce a friable wool.

- 19 -

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- 21 -

CLAIMS

1. A dressing material comprising a pharmacologically active agent entrapped in liposomes, the liposomes being encapsulated in a hydrocolloid matrix.
2. A dressing material according to claim 1 and further comprising a plasticiser in the hydrocolloid matrix.
3. A dressing material according to claim 2 wherein the plasticiser is glycerol or dimethylsulphoxide.
4. A dressing material according to any one of claims 1 to 3 wherein the hydrocolloid matrix is crosslinked.
5. A dressing material according to any one of claims 1 to 4 wherein the hydrocolloid matrix is an alginate matrix.
6. A dressing material according to claim 5 wherein the hydrocolloid matrix is cross-linked calcium alginate.
7. A dressing material according to any preceding claim in the form of a film, fibres, a clot or a foam.
8. A process for producing a dressing material as claimed in any one of claims 1 to 7 which process comprises
 - a) entrapping a pharmacologically active agent in liposomes and
 - b) encapsulating the liposomes in a hydrocolloid matrix.
9. A process according to claim 8 further comprising forming the dressing material into a film,

- 22 -

fibres, a clot or a foam and cross-linking the hydrocolloid matrix.

10. A process according to claim 8 or claim 9 further comprising dehydrating the dressing material.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB88/00723

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 L 15/03; A 61 K 47/00; A 61 K 9/00		
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁷</div> <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;">Classification System ¹</div> <div style="width: 65%;">Classification Symbols</div> </div> <div style="padding: 10px; text-align: center;"> IPC⁴ A 61 L, A 61 K, A 61 F, A 61 M </div> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸</div>		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP, A2, 0 199 362 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 29 October 1986 see page 5, 17-19, claims 12-15 <div style="text-align: center;">--</div>	1-10
X	Chemical Abstracts, volume 103, no. 26, 30 December 1985, (Columbus, Ohio, US), Komatsu Hideo et al: "Poultices con- taining drugs stabilized in liposomes", see page 358, abstract 220822e, & Jpn. Kokai Tokkyo Koho JP 60,152,414, 10 August 1985 <div style="text-align: center;">--</div>	1
A	EP, A2, 0 160 266 (TERUMO KABUSHIKI KAISHA) 6 November 1985 see the whole document <div style="text-align: center;">--</div>	1-10
A	WO, A1, 87/01587 (BIOCOMPATIBLES LIMITED) 26 March 1987 see the whole document	1-10
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">1st November 1988</div>		Date of Mailing of this International Search Report <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">15 DEC 1988</div>
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0199362	29-10-86	None	
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